Recombinant Human Thrombopoietin in Myelosuppressive Chemotherapy

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Recombinant human thrombopoietin (rhTPO) is a full-length glycosylated molecule that has been under evaluation in the setting of

Introduction

Myelosuppression is a major clinical problem in the management of cancer patients receiving cytotoxic therapy. The availability of recombinant myeloid growth factors, granulocyte colony-stimulating factor (G-CSF [Neupogen]), and granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukine, Prokine]) has reduced the duration of severe neutropenia.[1] More recently, focus has been directed to potential agents that may attenuate thrombocytopenia. The relationship between the severity of thrombocytopenia and the risk of bleeding complications is established[2].

Platelet transfusions, which may decrease the risk of severe bleeding complications, also carry potential risks, including transfusion reactions, transmission of infectious agents, graft-vs-host disease, and most importantly, alloimmunization. In the past decade, several cytokines with thrombopoietic potential, such as the interleukins (ILs) (IL-1, IL-3, IL-6, IL-11 [Interleukin 11, Neumega]), hybrid cytokine PIXY 321 (a GM-CSF/IL-3 fusion protein), and engineered chimeric growth factor receptor agonists (megakaryopoietin [Leridistim], promegapoietin [SC71858]) have been evaluated in clinical trials.[3-7] Some of these agents have shown thrombopoietic activity in vivo; however, their clinical utility has often been limited by toxicities.

Thrombopoietin, the ligand for the c-mpl receptors, is a primary regulator of platelet production in vivo. Since thrombopoietin was cloned,[7-11] two recombinant forms have been evaluated in clinical trials. The full-length glycosylated molecule is referred to as recombinant human thrombopoietin (rhTPO), and the truncated, pegylated version of the molecule is known as pegylated recombinant human megakaryocyte growth and development factor (MGDF). Both of these molecules have shown potent biologic effects in vivo in phase I/II clinical trials.[12-19]

Clinical trials of MGDF have been discontinued, however, because of the development of neutralizing antibodies and clinically significant thrombocytopenia in some cancer patients and normal donors receiving this agent. In early clinical trials, rhTPO, the full-length molecule, was found to have an excellent tolerability and a favorable safety profile, and is currently under clinical development. This article briefly reviews the clinical experience with rhTPO in cancer patients receiving myelosuppressive chemotherapy.

Clinical Studies With rhTPO

We assessed the safety and in vivo biologic effects of rhTPO in cancer patients receiving myelosuppressive chemotherapy in three clinical trials. The initial study investigated effects of rhTPO administered intravenously (IV) in a dose-escalated manner to sarcoma patients receiving AI (doxorubicin [Adriamycin] and ifosfamide [Ifex]) chemotherapy.[12-17] Recombinant human thrombopoietin (0.3-2.4 mg/kg) was administered 3 weeks prior to chemotherapy (as a single dose or two doses given 2 days apart) to examine its clinical tolerability and hematopoietic effects. Three weeks later, patients received high-dose AI (doxorubicin, 90 mg/m²; ifosfamide, 10 g/m²) without rhTPO (cycle 1). The second cycle of AI was followed by rhTPO (cycle 2) at the same doses. Because AI causes cumulative myelosuppression, cycle 1 served as an internal control for cycle 2, during which patients were expected to experience more thrombocytopenia than in the previous course.
**Prechemotherapy Phase of Study**

In the prechemotherapy phase of the study, rhTPO elicited an increase in circulating platelet count (1.3 to 3.6-fold) in a dose-dependent manner.[12] Although the increase in platelet count was evident beginning on day 4, the peak effect was observed on approximately day 12. The platelet response was sustained, with a gradual decrease to near baseline level around day 21, prior to chemotherapy administration. This sustained response may be related, in part, to the prolonged serum half-life (20 to 30 hours) of this glycosylated molecule. The platelets appeared normal in morphology and exhibited normal aggregation in response to various agonist stimuli. Bone marrow examination performed 1 week after rhTPO administration revealed a marked increase in the number of megakaryocytes. These cells appeared normal in morphology; some were very large and appeared mature with abundant cytoplasm (Figure 1). There was also a significant increase in the number of hematopoietic progenitor cells of multiple lineages in the marrow, and mobilization of these cells in the peripheral blood.[20] However, no major changes in peripheral white blood cell counts or hematocrit values were noted.

**Postchemotherapy Phase of Study**

In the postchemotherapy treatment phase, rhTPO was administered in different schedules[16]. Results showed that the schedule of rhTPO administration (ie, one, two, or seven doses) postchemotherapy did not have a consistent effect on reducing the depth of the platelet nadir; in some patients, however, thrombocytopenia was less severe in cycle 2 (with rhTPO) than in cycle 1 (without rhTPO). Several factors implied that earlier administration of rhTPO might attenuate myelosuppression associated with chemotherapy, including the length of the AI regimen (4 days) and its association with an early platelet nadir (around day 12), the late peak effect of rhTPO on platelets, and the biologic effects of rhTPO on progenitor cells and on marrow megakaryocytes. We therefore examined the effects of rhTPO administered both prior to and after chemotherapy (starting from day -1) as one predose and two postdoses. The findings supported the importance of earlier administration of rhTPO in order to reduce severe thrombocytopenia.

Our next trial in this setting aims to optimize the rhTPO schedule to reduce Al-induced cumulative thrombocytopenia.[21] Recombinant human thrombopoietin 1.2 µg/kg × 4 is administered as all predoses (ie, prechemotherapy), all postdoses (ie, postchemotherapy), or as pre/post doses (3/1 [ie, three predoses, one postdose], 2/2, or 1/3). So far, most of the patients who have received rhTPO starting from day -5 of chemotherapy (on days -5, -3, -1, and 4) have had higher platelet nadirs in cycle 2 (with rhTPO) than in cycle 1 (without rhTPO). The finding further supports the importance of timing of rhTPO in relation to chemotherapy to attenuate thrombocytopenia. This trial will also assess the effect of scheduling both predosing and postdosing of rhTPO on reducing the need for platelet transfusions.

The third trial investigated the safety and biologic effect of rhTPO administered subcutaneously (SC) to patients with gynecologic malignancies who are receiving high-dose carboplatin.[17] Patients received a single rhTPO dose (0.6-3.6 mg/kg) SC prior to chemotherapy. Three weeks later, patients received carboplatin at an area under the concentration-time curve[AUC] of 11) alone as a control cycle. The second carboplatin cycle was followed by rhTPO given every other day for four doses, since carboplatin causes a delayed nadir (around day 16). Sixteen patients, most of whom were heavily pretreated, received rhTPO in the dose-escalation phase of the study. Results showed that a single dose, administered SC, induced a dose-related increase in circulating platelet count, although the increase was not as high as that previously observed in chemotherapy-naive patients.

In the postchemotherapy phase, for all doses combined (0.6-3.6 µg/kg, n=16), the platelet nadir was higher in cycle 2 than in cycle 1 (mean platelet nadir, 53,000/µL vs 35,000/µL, P = .005). The duration of grade 3 thrombocytopenia was reduced from 6 days to 3 days (P = .002).[17]

In this trial, the optimal biologic dose was defined as the lowest active dose at which the platelet response reached a plateau. The 1.2 µg/kg dose was found to be the optimal biologic dose by this schedule and with this regimen. To assess further the efficacy of rhTPO in attenuating severe thrombocytopenia, 12 patients received rhTPO as secondary prophylaxis. Recombinant human thrombopoietin significantly reduced the need for platelet transfusions, particularly in patients who...
recombinant rhTPO at the optimal biologic dose (75% of patients in cycle 1 without rhTPO required transfusion vs 25% in cycle 2 with rhTPO), \( P = .013 \) (Figure 2). The treatment has been well tolerated without serious adverse events. No constitutional symptoms, fluid retention, major organ toxicities, or enhanced incidence of thrombosis have been observed in these trials.

**Discussion**

Results of these early clinical trials show that rhTPO is clinically safe and mediates potent biologic effects in vivo. The pharmacokinetics and pharmacodynamics, kinetics of platelet response, and biologic effects at the precursor level of rhTPO all suggest that the best rhTPO administration schedule will depend on the type of chemotherapy regimen being used and the kinetics of platelet nadir associated with that regimen. Our findings suggest that with a late-nadir regimen, such as single-agent carboplatin (Paraplatin), postdosing of rhTPO may be sufficient in decreasing the severity of thrombocytopenia. However, with early-nadir regimens, especially with the long regimen,[16] earlier administration (both pre- and postdosing) might be important for best amelioration of thrombocytopenia. An ongoing trial[16] is examining the importance of dose and schedule of rhTPO in achieving optimal biologic effect.

**Conclusions**

The potent biologic effects of rhTPO suggest several potential clinical applications for this novel cytokine, including prevention and management of thrombocytopenia associated with myelosuppressive cytotoxic treatment, stem/progenitor cell-supported myeloablative treatment, bone marrow failure conditions, congenital and acquired thrombocytopenias, and mobilization of progenitor cells. Recombinant human thrombopoietin may also be useful in facilitating harvesting of platelets for cryopreservation and subsequent transfusions in cancer patients as well as in certain non-oncology treatment settings. Future trials will further define the safety profile and the optimal role of this agent in various clinical conditions.

**References:**


